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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,706	BAUM ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on ~~02/24/1999~~ 8/23/01 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(4) because numerical reference characters have been used to designate different features in the drawings, Figures 1 and 2, while the brief description of the drawings uses lower case roman numerals when referring to different features in drawings of Figures 1 and 2. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 1-2 and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 use the phrase "water transport protein" where other claims and the specification use the term "water channel protein". It is noted that the term of art commonly used in the literature is water channel protein, thus it is not clear if applicant is using "water transport protein" due to additional functionality or if applicant is using the terms interchangeably. As written claims 1 and 2 are indefinite and unclear.

Claim 5 uses the term "engineered to secrete water unidirectrionally" when referring to "cells". The claim as written can be interpreted to mean that applicant's invention entails manipulating cells in a fashion where water can be secreted unidirectionally

exclusive of transducing cells with water channel protein genes. It is unclear whether the term "engineered" is used here as a substitute for transfected or transduced cells. Viz., unidirectional flow, the specification only teaches methods for ion transport (unidirectional or otherwise) that involves functional ion channels, thus does not shed light on the meaning of "engineered". For the purposes of examination the claim will be interpreted in the broadest sense including genetic manipulation. In addition because claims 6 and 7 depend from claim 5 they stand rejected.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass an artificial salivary gland comprising any cell (claims 1 and 3-7) or any transduced epithelial cells (claim 2 and 5-7) that can form a layer on a support surface, wherein said cells produce a water channel protein either inherently or because of transfection. The claims encompass an entire genus of subject matter (i.e. any cell or any epithelial cell) while the specification discloses only submandibular epithelial cells from rat that are transfected or human cell lines (HSG) that are used to coat a

support surface as two potential cell types that can be used to comprise an artificial salivary gland, while not disclosing an artificial salivary gland at all. *See infra* Section 3 (discussing lack of enablement for artificial salivary gland).

The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus.

The claims read on any cell that can form a layer on a support surface and that produces water transport protein. The specification discloses only one cell type – rat submandibular gland cells – as being amenable to transfection and expression of water transport channel protein and another cell type – HSG – as amenable to coating a support surface. Applicant does not disclose what other cells would function in the artificial salivary gland. For instance as between any cell and submandibular gland cells, there is no description as to what the shared characteristics are that would be necessary for a functional artificial salivary gland. For example what phenotypical characteristics are necessary to allow attachment to the support structure, what allows cells or epithelial cells to be more amenable to stable transfection, what are the certain ion channels that must necessarily be present in cells to be used in a functional artificial salivary gland and

what cells would contain necessary salivary gland cell-specific promoter elements that would be required for a functional artificial salivary gland.

In addition claim 6 includes an additional limitation that the cells of claims 1-5 produce an ion-transport protein (i.e. contain ion-transport channels). The lipid bilayer membrane of all (e.g. mammalian) cells contain ion-transport channels, thus ion-transport proteins, so that claim 6 would encompass virtually any cell that can form a polarized monolayer and that contains water channels; this would include virtually all epithelial cells from such diverse sources as intestinal, nasal, bronchial and salivary. Furthermore it is well established in the art that water secretion in epithelial cells is inextricably tied to ion-transport channels (i.e. Na^+, K^+, HCO_3^- and Cl^-), which are operationally tissue- or organ-specific (i.e. intestinal versus salivary).

Aside from the submandibular gland cells cited in the specification, there is not sufficient support in the specification that cells with features of claims 1-7 can function as a salivary gland thus the claims are rejected; Cell features include intact signaling systems such as required to regulate salivary fluid secretion, ability to form a polarized monolayer, responsiveness to different extracellular matrix components, ability to secrete ions or water unidirectionally or amenability to stable transfection.

3. Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim an artificial salivary gland *in vivo* acting device having a support, an attachment surface joined to the support, and joined to the attachment surface a layer or monolayer of cells (the monolayer being polarized: claims 4-6), that through expression of water channel proteins or ion channel proteins secrete water and ions unidirectionally. The cells can be any cells (claims 1, 2-4 and 6) or epithelial cells (claims 2 and 6-7) that express water channel proteins inherently (claims 1, 2-4 and 6) or the claims read on a gene therapy composition (claims 2 and 5-7).

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The invention is broad with the claims reading on use of any cell (claims 1, 3-6) or epithelial cell (claims 2 and 6) in an artificial salivary gland. Furthermore the claims encompass any cell or epithelial cell that either produce water channel proteins or ion transport proteins (claims 1, 3-6) or are transduced to express water channel or ion channel proteins (claims 2 and 6), where said cells are disposed on a water porous support to secrete water and ions unidirectionally. Furthermore the claims encompass any medium that is water porous to be used as a support for the cells. Moreover since the cells have to be transduced the invention

involves gene therapy (claims 2 and 5-7). Thus the claims are broad as they are drawn to effects *in vitro*, *in vivo*, gene therapy, polymers used in implantation and biocompatibility.

Nature of the invention. The invention involves gene therapy (claims 2 and 5-7), which is one of the most complex and unpredictable aspects of molecular biology/medicine. Specifically the claims are drawn to transfection of cells to express water channel or ion channel proteins and implantation of a device containing such cells for *in vivo* use. In addition the invention involves *in vivo* implantation of the artificial salivary device that would be comprised of autologous or allogeneic cells (claims 1, 3-4 and 6) that already produce water transport proteins or ion transport proteins (i.e. contain water channels for secretion of water or ion channels for transport of ions).

Unpredictability of the art. With regard to claims 2 and 5-7 gene therapy is extremely unpredictable. The ability of the cells transduced to express functional water channel proteins so that properly functional artificial salivary gland can be maintained in the body is dependent on multiple factors, such as type of cell, the maintenance of the heterologous gene (i.e. water channel protein gene), type of delivery method to introduce the gene of interest, immune rejection, etc. Tellingly, applicant uses adenoviral vectors in the examples disclosed and notes the problems of transient expression and induction of potent immune responses (Spec. p. 4 lines 3-10). *See also* Kmiec, American Scientist, 1999, Vol. 87: 240-147; Anderson, Nature, 1998, Vol. 392: 25-30; Verma et al., Nature, 1997, Vol. 389: 239-242. Given the unpredictable behavior of any cells or any epithelial cells expressing or transduced to express water channel proteins *in vivo*, it is impossible

to predict whether use of such cells will result in a functional *in vivo* artificial salivary gland.

With regard to claims 1, 3-4 and 6 there is unpredictability in that cells that are able to form a layer or a monolayer on the support surface provided would have to be then implanted contained in the artificial salivary gland and respond to the normal signaling machinery to secrete water or ions as necessary. For example red blood cells, which produce water channel proteins could be used but are not likely to function in an artificial salivary gland fashion. Furthermore, cells from disparate tissue types (e.g. eye, intestine and salivary gland) all contain water channels and ion channels for transport but not all would predictably function in an artificial salivary gland. There is nothing in the specification that teaches that various cell types would be able to grow, replicate and function whether the cells are allogenic or autologous.

As indicated in Baum, Principles of Saliva Secretion. (1993) N.Y. Acad. Sci. 694: 17-23, "Salivary gland are composed of highly differentiated epithelial cells...[with] distinct functional and anatomical regions." Baum at 17. In addition there ~~is~~ are complex neurotransmitter mechanisms involved in "All secretion from human salivary glands...". Id.

Furthermore implantation of an artificial salivary gland can have unexpected and serious inflammatory effects as a result of local tissue response to implants. In addition satisfactory functioning would reasonably depend on the adequacy of blood supply and level of neuronal stimulation involving complex and unpredictable cascades of signaling and receptors. See also, Aframian et al. Tissue compatibility of two biodegradable

tubular scaffolds implanted adjacent to skin or buccal mucosa in mice. Tissue Engineering, 8(4): 649-659 (Aug 2002) (citing the many difficulties with inflammatory responses to polymers not to mention allogneic graft cells and that future studies are necessary to address such concerns as appropriate model systems, implant ejection, acute and chronic inflammatory response).

State of the art. At the time of applicant's invention transplantation of mammalian salivary glands had been attempted but there were no examples of artificial salivary glands as envisioned by the applicant. In addition, to date the regulatory mechanisms underlying the functions of water channel proteins (i.e. salivary gland function and mechanisms) have not been elucidated. The closest type of art known were artificial salivary glands comprising an internal or external chamber that served as a reservoir for fluid that would be secreted through plastic tubes into the oral cavity.

Amount of guidance provided. First the specification discloses use of a recombinant adenovirus (AdhAQP1) to infect rats to enhance fluid secretion from rat submandibular gland cells that had previously been exposed to radiation. The specification does not actually use an artificial salivary gland device in effecting enhanced fluid secretion in the rat submandibular gland cells. The specification then suggests that use of human submandibular gland cell line (HSG) would be appropriate in an artificial salivary gland because HSG cells are useful targets for gene transfer methods and can utilize established salivary gland cell-specific promoter elements. The specification only discloses use of the HSG cells to show *in vitro* that such cells can form a layer on PLLA and PGA, which are water porous biodegradable polymer supports,

while noting that HSG cells inhere a phenotype that is highly responsive to different extracellular matrix components thus forming a monolayer on the support structure. The example actually does not involve implantation of the device so there is no guidance as to actual implantation of an artificial salivary gland. Nor is there any guidance as to what the important phenotypic characteristics are inherent in HSG cells that can be used in selecting other cells or epithelial cells for use in an artificial salivary gland.

Number of working examples. There are no working examples of an artificial salivary gland. The only examples provided are infection of whole animal with adenovirus and coating of support surfaces with HSG cells in vitro (i.e. expression of AQP1 in rat submandibular gland cells and seeding of HSG cells on PLLA and PGA).

Level of Skill in the art. The level of skill for this invention is high as it involves gene therapy and surgical skill in removal of cells as well as implantation. Concomitantly the level of unpredictability in the art is quite high with regards to transient expression of transduced genes and biocompatibility with regards to an immune response.

Given the above analysis of the factors that the courts have determined are critical in ascertaining whether the claimed invention is enabled, it is considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Conclusion

Claims 1-7 stand rejected for aforementioned reasons. The drawings require correction.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 703-305-4454. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

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July 28, 2003

DAVID GUZO
PRIMARY EXAMINER